REMARKS

Amendments in the claims

Following amendment herein, Claims 10–21 are pending in the present application, of which Claims 15–18 are presently withdrawn from consideration. Claims 1–9 were previously canceled. No increase in total number of claims or in number of independent claims results from the present amendment and no excess claim fees are believed payable.

Claims 10 and 19 are amended to remove the term "general" from the recitation of "general formula". This amendment clarifies Claims 10 and 19 and has no impact on the meaning and scope of the claims.

Claims 10 and 19 are further amended to move the recitation "or a salt thereof" to a different position in the claim. This amendment further clarifies Claims 10 and 19 by making it clearer that "a salt thereof" means a salt of the recited prodrug, not specifically of an R^2 or R^3 group.

Claim 10 is still further amended to recite that the at least one pharmaceutically acceptable carrier or adjuvant is selected from a Markush group of such carriers and adjuvants. Each member of the Markush group finds support in the specification as filed, at least at paragraph **[0060]**.

No new matter is added by the present amendment, and no change in inventorship is believed to result therefrom.

RESPONSE TO OFFICE ACTION DATED OCTOBER 16, 2008

1. Priority

The present Action acknowledges Applicant's claim for foreign priority based on a prior application filed in Germany on December 18, 2003. However, the Action determines the earliest effective filing date as to Claims 10–14 and 19–21 to be December 13, 2004. No explanation is given for denial of the benefit of priority for these claims. Applicant respectfully traverses this denial and requests a fuller explanation in the next action so that a reasoned argument for benefit of priority can be made.

2. Information disclosure statement

The Action contains the erroneous statement "None provided" in the section headed

"Information Disclosure Statement" (Action, p. 2). A check of the transaction history and image file wrapper in PAIR confirms that an IDS was indeed entered on April 15, 2008. Further, that IDS included submission of at least two of the documents listed in the Examiner's PTO-892 accompanying the present Action, namely the articles by Hacksell (1979) and Wikström (1985). The same IDS included submission of the article by Swart (1994) which is acknowledged in the Action as having been "provided by Applicant" (Action, middle of p. 4).

Proper consideration of the complete IDS dated April 15, 2008 and initialed copy of Applicant's Form PTO-1449 are respectfully requested.

2. Rejection under 35 U.S.C. §112, second paragraph

Claims 10–14 and 19–21 are rejected under 35 U.S.C. §112, second paragraph, as indefinite because the meaning of the term "general formula" is allegedly unclear. Specifically, the Examiner asserts that the term "general" is a broad term and therefore results in the rejected claims encompassing compounds in addition to compounds having the exact formula shown. Applicant respectfully disagrees with this interpretation and submits that the word "general" merely signifies that the recited formula is generic to more than one compound. However, inclusion of the word "general" is admittedly redundant, and for this reason the word is deleted by the present amendment. The present rejection is therefore now moot, and withdrawal of the present rejection is respectfully requested.

3. Rejection under 35 U.S.C. §102(b) over Swart

Claims 10, 11 and 14 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Swart *et al.* (1994) J. Anal. Toxicol. 18:71–77 ("Swart"). This rejection is respectfully traversed.

A claim is anticipated only if each and every element is found, either expressly or inherently described, in a single prior art reference. MPEP 2131.

As amended herein, Claim 10 is directed to a composition comprising at least one pharmaceutically acceptable carrier or adjuvant selected from the group consisting of fillers, disintegrants, binders, lubricants, stabilizers, flavors, anti-oxidants, preservatives, dispersants, buffers and electrolytes. The pharmaceutically acceptable carrier or adjuvant allegedly

present in Swart, namely water, does not fall into any of the recited categories in this Markush group. Accordingly, Claim 10 and Claims 11 and 14 dependent therefrom are not anticipated by Swart. Therefore, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

4. Rejection under 35 U.S.C. §102(b) over den Daas

Claims 10, 12 and 13 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by den Daas *et al.* (1990) Naunyn-Schmiedeberg's Arch. Pharmacol. 342:655–659 ("den Daas"). This rejection is respectfully traversed.

The alleged anticipation by den Daas arises through a misinterpretation of the term "general formula", which the Examiner appears to read as permitting additional substitution of the amino group. By amendment herein the word "general" is deleted, and no such misinterpretation is now possible. Claim 10 recites prodrugs that are N-monosubstituted (specifically N-propyl-) amino compounds. The compounds cited in den Daas are all N,N-disubstituted amino compounds and therefore do not anticipate Claim 10 or Claims 12 or 13 dependent therefrom. Therefore, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

5. Rejection under 35 U.S.C. §103(a) over Hacksell in view of Wikström and Rodenhuis

Claims 10–12, 14 and 19–21 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hacksell *et al.* (1979) J. Med. Chem. 22(12):1469–1475 ("Hacksell") in view of Wikström *et al.* (1985) J. Med. Chem. 28:215–225 ("Wikström") and Rodenhuis (2000) Dissertation, Rijksuniversiteit Groningen titled "New, centrally acting dopaminergic agents with an improved oral bioavailability: synthesis and pharmacological evaluation" ("Rodenhuis"). This rejection is respectfully traversed.

5.1. Claims 19–21

Claims 19–21 are drawn to prodrugs of (S)-2-N-propylamino-5-hydroxytetralin. The present Action alleges that it would have been obvious to select racemic 2-N-propylamino-5-hydroxytetralin from Hacksell, perform enantioseparation per Wikström to provide the (S)-enantiomer, and prepare prodrugs of the (S)-enantiomer per Rodenhuis.

5.1.1. Lack of motivation to select 2-N-propylamino-5-hydroxytetralin from Hacksell

Under *KSR International Co. v. Teleflex Inc*, 127 S. Ct. 1727 (2007), a claimed invention is considered obvious if the differences between the invention of the claim and the prior art are such that that subject matter of the invention of the claim as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art..

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." MPEP 2143. Here, the Examiner cites Hacksell as providing motivation to select racemic 2-N-propylamino-5-hydroxytetralin for further investigation. Specifically, the Action (p. 8, lines 12–14) cites Hacksell as allegedly teaching "that racemic 2-N-propylamino-5-hydroxytetralin is a potent dopamine agonist ... which is acknowledged by Applicant," citing paragraphs **[0007]–[0008]** of the present specification. For the record, Applicant respectfully disagrees with the Examiner's assertion that Applicant acknowledges any such potency of racemic 2-N-propylamino-5-hydroxytetralin. Specifically, paragraph **[0008]** states only that "[a] particular dopaminergic activity was demonstrated for the racemic 2-N-propylamino-5-hydroxytetralin." (emphasis added). Furthermore, nothing in paragraphs **[0007]–[0008]** suggest that racemic 2-N-propylamino-5-hydroxytetralin is a potent dopamine agonist. In fact, paragraph **[0008]** goes on to state that "the agonistic activity of the substance with an ED_{50} of 40 nM/kg is only moderate and that the AUC and the half life are short in comparison with the other evaluation compounds" (emphasis added).

Applicant further disagrees with the Examiner's assertion that one of ordinary skill would have been motivated to formulate compounds and compositions containing 2-N-propylamino-5-hydroxytetralin. For example, Swart *et al.* (1993) Toxicol. Meth. 3:279–290, of record in the present application, describes the racemate of 2-N-propylamino-5-hydroxytetralin as a "rotigotine metabolite with weaker dopaminergic activity." Swart concludes that the N-dealkylated metabolites of rotigotine have a dopaminergic activity too weak for them to have therapeutic relevance. Even the data provided by Hacksell (Table I therein) show that aminotetralins with N,N-dialkylation are the most active. Therefore, Applicant respectfully submits that the teaching in the art is such that one of ordinary skill would have been motivated not to select an N-dealkylated compound such as racemic 2-N-

propylamino-5-hydroxytetralin, but instead to select an N,N-dialkylated compound.

In an attempt to rebut the preference in the art for N,N-dialkylated compounds, the Examiner states that "racemic 2-N-propylamino-5-hydroxytetralin demonstrates significant agonistic activity" and is "significantly more potent than apomorphine" (Action, p. 8, line 14 – p. 9, line 2). It is not clear exactly how a comparison to apomorphine relates to the present rejection, but any significance that could be accorded to this result is diminished by the fact that at least eighteen other tested compounds were also more potent than apomorphine (Hacksell, Table 1). Thus motivation to specifically select 2-N-propylamino-5-hydroxytetralin from Hacksell for enantiomeric separation per Wikström and for formulation of prodrugs per Rodenhuis has not been demonstrated by the Examiner.

Under *ATD Corporation v. Lydall, Inc.*, 159 F.3d 534, 48 USPQ2d 1321 (Fed. Cir. 1998), obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the claimed invention. Based on the foregoing arguments, Applicant submits that the present rejection is based on nothing more than improper hindsight reconstruction. As stated in *KSR, supra*, "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." Because one of ordinary skill would not have been motivated to select racemic 2-N-propylamino-5-hydroxytetralin from the disclosure of Hacksell, Applicant submits that the present rejection is improperly based on the teachings of Applicant's own specification. Therefore, at least for this reason, Applicant submits that no *prima facie* case of obviousness has been established.

5.1.2. No reasonable expectation of success

Even if, *arguendo*, motivation existed to select 2-N-propylamino-5-hydroxytetralin from Hacksell for enantiomeric separation per Wikström and prodrug formulation per Rodenhuis, the predictability of outcome or reasonable expectation of success required to sustain a *prima facie* case of obviousness is lacking.

Reasonable expectation of success has long been a required criterion for a *prima facie* case of obviousness. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In recently redefining the standards for determining obviousness, the U.S. Supreme Court in *KSR, supra* has confirmed that "[t]he combination of familiar elements according to known

methods is likely to be obvious when it does no more than yield predictable results" (emphasis added); see also MPEP 2143.01.III: "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art" (emphasis in original).

Here, in combination with Hacksell, the Examiner cites Wikström as allegedly teaching "enantiomeric separation of related aminotetralins to increase dopamine agonist activity." Specifically, the Examiner cites Wikström as having investigated the potency of "structurally and functionally related 5-hydroxy-2-(N,N-di-n-propylamino)tetralin (Action, p. 9, lines 8–9). However, as shown above, the art clearly distinguishes N,N-dialkylated compounds from the N-dealkylated compounds of the present invention. Therefore, one of skill could not have reasonably expected to achieve the same level of success with an N-dealkylated compound, and therefore would not have applied teachings relating to a N,N-dialkylated compound to 2-N-propylamino-5-hydroxytetralin with any reasonable expectation of success.

Moreover, even if one of skill in the art would have expected one of the enantiomers to have a higher activity than the racemate, it could not have been predicted that specifically the (S)-enantiomer would exhibit the pronounced and functional D3 selectivity shown in Table 2 of the present specification. It also could not have been predicted that (S)-2-N-propylamino-5-hydroxytetralin would show purely agonistic activity. Therefore, Applicant submits that even if one of skill in the art would have been motivated to select 2-N-propylamino-5-hydroxytetralin for enantioseparation (which is not admitted herein), the results could not have been predicted. Therefore, Applicant submits, that for this additional reason, no *prima facie* case of obviousness has been established.

Likewise, even if one of skill in the art would have expected improvement in oral bioavailability by formulation of prodrugs per Rodenhuis, it could not have been predicted that specifically (S)-2-N-propylamino-5-hydroxytetralin would be an attractive candidate for a prodrug search. Therefore, Applicant submits that even if one of skill in the art would have been motivated to select 2-N-propylamino-5-hydroxytetralin for enantioseparation and prodrug formulation (which is not admitted herein), the results could not have been predicted. Therefore, Applicant submits, that for this additional reason, no *prima facie* case of obviousness has been established.

5.2. Claims 10–12 and 14

Claims 10–12 and 14, drawn to compositions containing (S)-2-N-propylamino-5-hydroxytetralin or a prodrug thereof, are rejected on similar grounds to Claims 19–21, with the further argument that Hacksell and Wikström each disclose dissolution in saline, characterized by the Examiner as a pharmaceutically acceptable carrier or adjuvant.

By amendment of Claim 10 herein, the pharmaceutically acceptable carrier or adjuvant is specified to be of a category that does not include a solvent such as saline. Therefore this further argument is moot and Claims 10–12 and 14 are non-obvious over Hacksell in view of Wikström and Rodenhuis for the same reasons (articulated above) that Claims 19–21 are nonobvious over this same art combination.

Withdrawal of the present 35 U.S.C. §103(a) rejection of Claims 10–12, 14 and 19–21 is respectfully requested.

6. Rejection under 35 U.S.C. §103(a) over Hacksell in view of Wikström and Rodenhuis and further in view of Jansen

Claim 13 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hacksell in view of Wikström and Rodenhuis as applied to claims 10–12 and 14, in further view of Jansen *et al.* (1991) Naunyn-Schmiedeberg's Arch. Pharmacol. 343:134–142 ("Jansen"). Jansen is cited as allegedly teaching transdermal administration to overcome a first-pass metabolism effect.

However, for reasons set forth above, a *prima facie* case of obviousness of Claim 10 is not sustainable. Claim 13 depends from Claim 10 and is therefore likewise non-obvious over Hacksell in view of Wikström and Rodenhuis. Notwithstanding any disclosure in Jansen relevant to transdermal administration, "[i]f an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious" MPEP 2143.03.

Withdrawal of the present ground of rejection is respectfully requested.

7. Conclusion

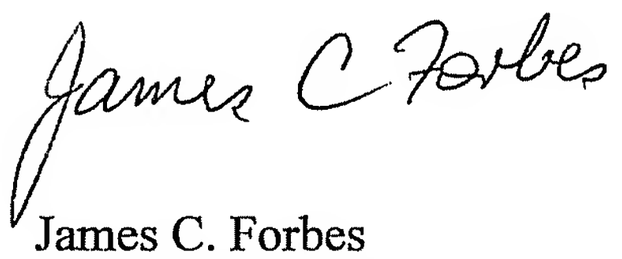
It is believed that all of the stated grounds of rejection are properly traversed, accomodated or rendered moot herein. Applicant therefore respectfully requests that the Examiner consider and withdraw all presently outstanding rejections. It is believed that a full

and complete response has been made to the present Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

HARNESS, DICKEY & PIERCE, P.L.C.



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